# Y RNA fragment in extracellular vesicles confers cardioprotection via modulation of IL-10 expression and secretion.

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**Public Summary:**
Cell therapy with cardiosphere-derived cells (CDCs), adult cardiac stem cells, is clinically effective in regenerating the injured human heart after heart attack. These beneficial effects are mediated via nanoparticles that CDCs secrete, called extracellular vesicles (CDC-EVs). CDC-EVs contain lipids, proteins, DNA and several RNA species. We questioned whether a short non-coding RNA species of unknown function within CDC-EVs contribute to the cardioprotection effect mediated by CDCs. We found that the most abundant RNA species in CDC-EVs is a Y RNA fragment (EV-YF1). EV-YF1 is highly abundant in CDC-EVs secreted from CDCs showing a high level of efficacy in terms of cardiac regeneration after heart attack. Using different techniques, we observed EV-YF1 was directly transferred from CDCs to target cells, like macrophages, via CDC-EVs. In addition, EV-YF1, when expressed at high levels in macrophages, induces the expression of an anti-inflammatory cytokine, IL-10. In vitro experiments, in which rat cardiomyocytes and rat macrophages were cultured together, have shown that macrophages with high levels of EV-YF1 protected cardiomyocytes from induced cell death. This protective effect was mediated by the anti-inflammatory cytokine IL-10. In in vivo experiments, we induced heart attack in rats by blocking blood flow to the heart for 45 min and then treated the animals by injecting intracoronary EV-YF1 10 min after reallowing blood flow. Treated animals showed a decrease in heart injury. EV-YF1, highly expressed in CDC-EVs, confers cardioprotection after heart attack via regulation of the anti-inflammatory cytokine IL-10. This discovery highlights the potential importance of a new RNA species, of unknown function, present in CDC-EVs, above and beyond the usual suspects (e.g., microRNAs and proteins).

**Scientific Abstract:**
Cardiosphere-derived cells (CDCs) reduce myocardial infarct size via secreted extracellular vesicles (CDC-EVs), including exosomes, which alter macrophage polarization. We questioned whether short non-coding RNA species of unknown function within CDC-EVs contribute to cardioprotection. The most abundant RNA species in CDC-EVs is a Y RNA fragment (EV-YF1); its relative abundance in CDC-EVs correlates with CDC potency in vivo Fluorescently labeled EV-YF1 is actively transferred from CDCs to target macrophages via CDC-EVs. Direct transfection of macrophages with EV-YF1 induced transcription and secretion of IL-10. When cocultured with rat cardiomyocytes, EV-YF1-primed macrophages were potently cytoprotective toward oxidatively stressed cardiomyocytes through induction of IL-10. In vivo, intracoronary injection of EV-YF1 following ischemia/reperfusion reduced infarct size. A fragment of Y RNA, highly enriched in CDC-EVs, alters Il10 gene expression and enhances IL-10 protein secretion. The demonstration that EV-YF1 confers cardioprotection highlights the potential importance of diverse exosomal contents of unknown function, above and beyond the usual suspects (e.g., microRNAs and proteins).